Original Article

Impact of Smoking on Biological Treatment Response in Patients From the German Severe Asthma (GAN) Registry

Slagjana Stoshikj, MD[a], Leonie Biener, MD[b], Andreas Renner, MD[a], Christina Bal, MD[a], Jonas Brugger, MSc[c], Christoph Krall, PhD[c], Katrin Milger, MD[d], Christian Schulz, MD[e], Margret Jandl, MD[f], Rainer Ehmann, MD[g], Olaf Schmidt, MD[h], Roland Buhl, MD[i], Eckard Hamelmann, MD[j], Christian Taube, MD[k], Stephanie Korn, MD[l], Dirk Skowasch, MD[b,*], and Marco Idzko, MD[a,*] *Vienna, Austria; and Bonn, Munich, Regensburg, Hamburg, Stuttgart, Koblenz, Mainz, Bielefeld, and Essen, Germany*

What is already known about this topic? Ex-smokers with severe asthma and over 10 pack-years are excluded from clinical trials for biologics. Consequently, the impact of smoking and smoking cessation on the course of asthma in patients undergoing biologic therapy remains uncertain.

What does this article add to our knowledge? Patients with a smoking history can profit from biologic therapy as well as never-smokers. Furthermore, this study provides valuable insights into valuable clinical characteristics relevant to asthma management with biologics among patient groups with varying pack-year counts.

How does this study impact current management guidelines? Ex-smokers with severe asthma may be eligible for biologics as well as never-smokers and should be included in randomized trials.

[a]Clinic of Internal Medicine II—Department of Pneumology, Medical University of Vienna, Vienna, Austria
[b]Department of Internal Medicine II—Pneumology, University Hospital Bonn, Bonn, Germany
[c]Department for Medical Statistics, Informatics and Intelligent Systems, Medical University of Vienna, Vienna, Austria
[d]Department of Medicine V, University Hospital, LMU Munich, Comprehensive Pneumology Center Munich (CPC-M), Member of the German Center for Lung Research, Munich, Germany
[e]Respiratory Department, University Hospital Regensburg, Regensburg, Germany
[f]Hamburger Institut für Therapieforschung, Hamburg, Germany
[g]Outpatient Pneumology with Allergy Centre (BAG), Stuttgart, Germany
[h]Pneumologische Gemeinschaftspraxis und Studienzentrum KPPK, Koblenz, Germany
[i]Pulmonary Department, Mainz University Hospital, Mainz, Germany
[j]Department of Pediatrics, Children's Center Bethel, University Hospital OWL, University Bielefeld, Bielefeld, Germany
[k]Department of Pulmonary Medicine, University Hospital Essen, Ruhrlandklinik, Essen, Germany
[l]Thoraxklinik Heidelberg and IKF Pneumologie, Heidelberg and Mainz, Mainz, Germany
*These authors contributed equally to this work and share senior authorship.
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Corresponding author: Marco Idzko, MD, Internal Medicine II, Department of Pulmonology, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria. E-mail: marco.idzko@meduniwien.ac.at.
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Abbreviations used
ACQ- Asthma Control Questionnaire
ACT- Asthma Control Test
AE- Acute exacerbation
BARS- Biologics Asthma Response Score
BMI- Body mass index
CI- Confidence interval
COPD- Chronic obstructive pulmonary disease
DLCO- Diffusing capacity of the lungs for carbon monoxide
ExS- Ex-smokers
FeNO- Fraction of exhaled nitric oxide
FEV1- Forced expiratory volume in 1 second
FVC- Forced vital capacity
GAN- German Asthma Network
GINA- Global Initiative for Asthma
ICS- Inhaled corticosteroids
mAQLQ- Mini—Asthma Quality of Life Questionnaire
MEF- Mean expiratory flow
mOCS- Maintenance oral corticosteroids
NS- Never smokers
OCS- Oral corticosteroids
OR- Odds ratio
PBEC- Peripheral blood eosinophil count
PEF- Peak expiratory flow
py- Pack-years
Rtot- Resistance
RV- Residual volume
TLC- Total lung capacity

BACKGROUND: Clinical studies of biologics in severe asthma exclude smokers or ex-smokers (ExS) with over 10 pack-years (py). Thus, the effectiveness of this therapy in ExS with severe asthma is not well understood.
OBJECTIVES: To assess the impact of smoking on clinical efficiency of biologics in patients with severe asthma from the German Asthma Net, a comprehensive international registry.
METHODS: This analysis included 1129 patients (55.8% female, mean age: 53.82 ± 14.67 years), of whom 56% were never-smokers (NS), whereas 44% were ExS (<10 py: 22.9%, 10-20 py: 10.3%, and >20 py: 10.6%). They received benralizumab (38.3%), dupilumab (28.9%), mepolizumab (18.3%), omalizumab (14%), or reslizumab (0.5%).
RESULTS: Biologic therapy significantly improved asthma control, measured by change in Asthma Control Test, Asthma Control Questionnaire-5, and Mini—Asthma Quality of Life Questionnaire, lung function, reduced exacerbations, and daily oral prednisolone dose in all patients at week 52. Of note, no significant differences in asthma control between NS and ExS at week 52 ($P = .48$, .09, and .15, respectively) were observed. Also, lung function improvement (forced expiratory volume in 1 second, forced vital capacity, total lung capacity, peak expiratory flow, mean expiratory flow at 50%, $P > .05$), and reduction in acute exacerbation ($P = .8$) and oral corticosteroid doses ($P = .15$) were comparable in NS and ExS. Markers of type 2 inflammation, such as fraction of exhaled nitric oxide and blood eosinophils, decreased in ExS similar to NS ($P = .29$ and $P = .48$, respectively).
CONCLUSION: ExS with severe asthma experienced similar improvements in asthma control, exacerbations, lung function, and biomarkers as NS after 1 year of biologics, suggesting that severe asthmatics even with a substantial smoking history can benefit from biologic therapy. **(J Allergy Clin Immunol Pract 2025;13:1125-38)**

Key words: *Severe asthma; Registry; Smoking; Pack-years; Biologics; Asthma control; Lung function; Biomarkers; Exacerbations*

Over 300 million people worldwide are living with asthma, and approximately 3% to 10% of them have a severe form of the disease.[1] It has been observed that patients with asthma tend to have a higher smoking history rate, up to 46%, than the general population.[2] Smoking not only increases the risk of developing asthma but also leads to impaired response to corticosteroid therapy, poorer asthma control, more frequent exacerbations, and a higher overall mortality rate.[3] This results from the complex interplay between smoking and asthma pathogenesis, potentially leading to a distinct phenotype in patients with chronic obstructive pulmonary disease (COPD).[4]

Severe asthma, as defined by the European Respiratory Society and the American Thoracic Society, is a condition that requires treatment with high-dose inhaled corticosteroids (ICS), as well as a second controller and/or systemic corticosteroids, to be controlled or which remains uncontrolled despite this therapy.[5] Biologics significantly improve asthma control, reduce exacerbation frequency, enhance lung function, and yield positive biomarker outcomes without safety concerns for patients with severe asthma. However, all previous randomized trials excluded individuals with a smoking history exceeding 10 pack-years (py) because of the concern of possible COPD influencing the results.[6-10] In patients with adult-onset asthma, a smoking history of over 10 py is linked to accelerated lung function decline.[11] Another study found that smoking increases asthma severity, with an odds ratio (OR) of 1.4 per 10 py.[12] In addition, in patients with severe asthma, a smoking history of ≥10 py is associated with airway eosinophil activation, autoimmunity toward eosinophils and macrophages, and a reduced response to corticosteroids.[13] Real-world asthma studies involving biologics include individuals with a smoking history.[14-20] However, the number of ex-smokers (ExS) in these studies was limited, and there was no comparison of outcomes based on smoking history, leaving the influence of the py count particularly unclear. Our main goal was to determine whether biologics benefit these patients similar to never-smokers (NS). Our secondary objective was to explore potential differences in clinical characteristics relevant to asthma management among patient groups with varying py counts.

METHODS

The German Asthma Net (GAN) prospective registry has been enrolling patients with severe asthma since December 2011.[21,22] As of December 2021, the registry included 2478 patients aged over 6 years from various centers, including asthma referral centers and office-based pulmonologists primarily in Germany and Austria. The GAN registry received approval from the Ethics Committee of the Medical University of Vienna (EK Number 1849/2019), University of Mainz, and other respective local ethics committees. It was conducted in compliance with the Declaration of Helsinki, with each patient providing informed consent before participating in the registry. The study was registered at ClinicalTrials.gov (NCT06035289).

Objectives

We conducted an analysis to evaluate how smoking status influences asthma control, quality of life, exacerbations, oral corticosteroid (OCS) use, lung function, and T2 biomarkers after 16 and 52 weeks of treatment with biologics, prescribed in accordance with current clinical guidelines.

Study population and data collection

We focused on patients treated with omalizumab, mepolizumab, benralizumab, reslizumab, or dupilumab, comparing NS with ExS. We included patients with known smoking status and py count. One py equated to smoking 20 cigarettes daily for a year. We evaluated various patient characteristics, including demographics, medical history, medications, comorbidities, and disease characteristics, such as Global Initiative for Asthma (GINA) asthma control, Asthma Control Questionnaire (ACQ)-5, Asthma Control Test (ACT), Mini−Asthma Quality of Life Questionnaire (mAQLQ), individual symptoms, and exacerbation rates. In addition, we examined lung function values, including resistance (Rtot), forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), peak expiratory flow (PEF), maximal expiratory flow at 25%, 50%, and 75% (MEF25, MEF50, and MEF75, respectively), residual volume (RV), total lung capacity (TLC), reversibility, and diffusing capacity of the lungs for carbon monoxide (DLCO). Biomarkers such as fractional exhaled nitric oxide (FeNO), IgE, and peripheral blood eosinophil count (PBEC) were also assessed.

Patients with asthma were considered to have their condition under control if they met one of the following criteria: an ACT score >20, ACQ-5 score <1.5, or met the control criteria according to GINA, which required ≤2 daytime symptoms per week, no nighttime waking due to asthma, ≤2 reliever uses per week, and no activity limitation due to asthma.[23] Health-related quality of life was evaluated using an mAQLQ threshold >5.4 for better quality of life.

Outcomes

Significant clinical improvement was defined as a patient having an increase in ACT score of ≥3 points,[24] an ACQ-5 decrease of >0.5 points, an mAQLQ increase of >0.5 points,[25] a decrease in acute exacerbation (AE) rate, or OCS usage of ≥50%. In addition, a clinically significant improvement in lung function was defined as an increase in FEV1 ≥100 mL.[25] Exacerbations were characterized as a worsening of asthma symptoms that necessitated the administration of systemic glucocorticoids for ≥3 days, doubling the ongoing OCS dose, hospitalization, or emergency department treatment. In addition, we used the Biologics Asthma Response Score (BARS), which integrates changes of exacerbations, OCS, ACT, and optionally FEV1 over 1 year. Each of these categories contributes with 2, 1, or 0 points to the score (reduction of exacerbations ≥ 75%, 50%-74%, or <50%; daily OCS dose reduction ≥ 75%, 50%-74%, or <50%; and ACT increase ≥ 6 or improvement of ≥ 3 with result ≥ 20, improvement of 3-5 and score ≤ 20, or improvement of < 3). The derived score BARS−Lung function (BARS-L) includes an increase of FEV_1 ≥ ml 100 mL and FEV_1 ≥ 80%, an increase of FEV_1 ≥ ml 100 mL and FEV_1 ≤ 80%, or otherwise. The score was calculated in patients with complete data on all the above parameters. Asthma remission was defined as ACT score ≥ 20, no exacerbations, and no OCS use over 12 months.[26]

Statistical analysis

We present baseline data as mean ± standard deviation for normally distributed data, whereas for non-normally distributed data, we provide the median and interquartile ranges. Categorical data are expressed as numbers and/or percentages.

To assess differences at baseline between NS and ExS grouped by py, we used pairwise *t* tests or Mann-Whitney *U* tests for numeric variables according to their distribution and the χ^2 test for categorical variables.

We considered *P* values less than .05 to be statistically significant and *P* values less than .001 as highly statistically significant.

To investigate the relationship between treatment success and the number of py, we used linear models for each endpoint. The difference from the baseline score at 16 weeks or 52 weeks after starting biologics served as the dependent variable, with smoking history categorized into groups (NS, ExS, <10, 10-20, and >20 py), and the type of medication as the explanatory variable. In addition, the models were adjusted for age, sex, and the baseline value of the respective endpoint. We conducted analyses of variance and *post hoc* pairwise comparisons between NS and different smoking groups. In all cases of comparing smoking history, NS was used as the reference group. We also calculated contrast estimates to compare NS with ExS.

For binary or categorical endpoints, we used binary logistic or ordinal logistic regression models following the same approach. Point estimates and confidence intervals (CIs) reported in the tables refer to the ORs. To evaluate the treatment effect, we used the actual outcome at 16 weeks or 52 weeks with baseline values as covariate.

In certain cases, linear models were computed using the logarithm of the endpoint to better meet the normality assumption. In these instances, zero values were defined as half of the minimum of the remaining values for the logarithm to be defined. For all linear models, separate contrast estimates for the average treatment effect for each respective smoking history group versus NS were calculated. BARS was compared between NS and ExS by Mann-Whitney *U* tests.

No corrections for multiple testing were applied; therefore, all *P* values are of a descriptive nature. The statistical analysis was carried out using R, version 4.2.2 or higher (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Cohort description

A total of 1129 patients received biologics, which included benralizumab (38.3%), dupilumab (28.9%), mepolizumab (18.3%), omalizumab (14%), or reslizumab (0.5%), and were subsequently categorized by smoking habits. At week 16, data were available for 826 patients (250 lost to follow-up and 53 included within 16 weeks before the last record date). Follow-up at week 52 included 500 patients (422 lost to follow-up and 207 included within 52 weeks before the last record date). The baseline demographic and clinical characteristics are presented in Table I. The average age was 53.8 ± 14.7 years, with 55.8% being female. Among the patients, 56% were NS, and 44% were ExS with an average smoking history of 14.6 ± 16.1 py. At the start of the study, 27 patients (2.39%) were identified as active smokers. Of these, 17 returned for the 16-week visit and 11 for the 52-week visit. Smoking status was documented after 52 weeks for only 144 patients. Among these, 4 were active smokers at baseline, and after 52 weeks, 1 patient was still smoking. When comparing the 27 baseline smokers with NS, no differences were observed in ACT or FEV1 improvement. However, these findings lack statistical power due to the small sample size. The mean ACT score

TABLE I. Selected baseline demographic and clinical characteristics of the patients treated with biologic therapy, stratified by smoking status

Parameter	All	NS	ExS <10 py	*P* value vs NS	ExS 10-20 py	*P* value vs NS	ExS >20 py	*P* value vs NS
Patients, n (%)	1129	633 (56)	259 (22.9)		117 (10.4)		120 (10.6)	
Age (y), mean ± SD	53.8 ± 14.7	52.4 ± 16.3	53.2 ± 13.1	.45	57 ± 11.6	**.002**	59.4 ± 8.1	**<.001**
Current age ≥18 y, n (%)	1092 (96.7)	598 (94.5)	258 (99.6)	**.001**	117 (100%)	**.02**	119 (99.2)	**.02**
Female, n (%)	630 (55.8)	373 (58.9)	143 (52.2)	.34	65 (55.6)	.56	49 (40.8)	**<.001**
BMI (kg/m^2), mean ± SD	27.7 ± 6.2	26.8 ± 6.1	28.4 ± 6.0	**<.001**	28.7 ± 6.0	**.003**	29.8 ± 6.6	**<.001**
Pack-years, mean ± SD	14.6 ± 16.1		3.9 ± 2.7		14.1 ± 3.7		38.0 ± 15.7	
Duration of smoking in ExS (y), mean ± SD	17.3 ± 11.0		10 ± 6.4		20 ± 8.2		30 ± 7.7	
Years since asthma diagnosis (n = 784)*	20.2 ± 16.3	21.9 ± 16.7	19.1 ± 15.6	**.04**	18.1 ± 15.6	.06	15.4 ± 14.8	**<.001**
Early onset (≤12 y), n (%)	325 (28.8)	195 (30.8)	72 (27.8)	.23	28 (23.9)	.16	30 (25.0)	.32
Predominantly allergic asthma form, n (%) (n = 144)*	61 (42.4)	33 (44)	14 (43.8)	1.00	9 (34.6)	.55	5 (45.6)	1.00
High-dose ICS/LABA ± LAMA, n (%)	1040 (92.1)	580 (91.6)	243 (93.8)	.49	111 (94.9)	.41	106 (88.3)	.22
OCS, n (%)	525 (46.5)	303 (47.9)	107 (41.3)	.07	58 (49.6)	.86	57 (47.5)	.97
Daily equivalent prednisolone dose (mg/d)	14.7 ± 13.5	15.5 ± 14.5	14.0 ± 13.4	.33	14.7 ± 11.8	.69	12.0 ± 9.9	.07
Biologics in the past, n (%)	259 (22.9)	158 (25.0)	59 (22.8)	.52	14 (12.0)	**.02**	28 (23.3)	.86
AEs in the last 12 mo								
None, n (%)	68 (6)	41 (6.5)	16 (6.2)	.13	6 (5.1)	.83	5 (4.2)	.74
1×/y, n (%)	153 (13.6)	80 (12.6)	43 (16.6)		17 (14.5)		13 (10.8)	
≥1×/y, but <1×/mo, n (%)	629 (55.7)	351 (55.5)	144 (55.6)		67 (57.3)		67 (55.8)	
≥1×/mo, n (%)	184 (16.3)	110 (17.4)	30 (11.6)		21 (18.0)		23 (19.2)	
AEs in the last 12 mo, n, median (IQR) (n = 130)*	3 (1-4)	3 (1-4)	3 (1-5)	.97	3 (2-4)	.88	3.5 (2-9.75)	.95
Asthma control								
Controlled, n (%)	65 (5.8)	31 (4.9)	27 (10.4)	**.01**	3 (2.6)	**.01**	4 (3.3)	.25
Partially controlled, n (%)	138 (12.2)	88 (13.9)	33 (12.7)		6 (5.1)		11 (9.2)	
Uncontrolled, n (%)	924 (81.8)	512 (80.9)	199 (76.8)		108 (92.3)		105 (87.5)	
ACT score, mean ± SD (n = 941)*	13.4 ± 5.2	13.6 ± 5.3	14.1 ± 5.4	.31	12.0 ± 4.4	**.004**	11.8 ± 4.5	**<.001**
ACQ-5 score, mean ± SD (n = 129)*	3.0 ± 1.4	3.0 ± 1.4	2.7 ± 1.1	.73	3.1 ± 1.3	.588	3.6 ± 1.4	.581
mAQLQ score, mean ± SD (n = 127)*	3.6 ± 1.2	3.6 ± 1.2	3.7 ± 1.3	.89	3.4 ± 1.0	.67	3.3 ± 1.0	.89
Lung function								
FEV1 (L), median [IQR] (n = 1060)*	1.8 [1.34, 2.5]	1.9 [1.4, 2.5]	1.9 [1.5, 2.6]	.09	1.7 [1.2, 2.4]	.11	1.6 [1.1, 2.2]	<.001
% predicted (n = 1064)*	64 [48, 78]	66 [50, 79]	63 [51, 82]	.96	62.7 [45. 2.8]	.16	53 [38.2, 67.9]	<.001
FVC (L), median [IQR], (n = 140)*	3.1 [2.4, 3.8]	3.1 [2.4, 3.8]	2.9 [2.5, 3.7]	.86	3 [2.5, 3.7]	.52	2.5 [2.1, 3.4]	**.04**
% predicted (n = 140)*	82 [67.5, 95.5]	82 [67.5, 95.5]	84.5 [72.8, 97]	.26	90 [77, 101]	**.03**	75.5 [65.5, 85.8]	.32
FEV1% FVC, mean ± SD (n = 138)*	68.8 ± 15.5	71.2 ± 15.3	67.3 ± 18.1	.64	66.1 ± 12.8	.47	64.1 ± 13.9	.48
FEV1 reversibility (mL), mean ± SD (n = 64)*	195 [97.5, 357.5]	195 [97.5, 357.5]	155 [87.5, 255]	.11	180 [85, 210]	.09	190 [105, 430]	.79
FEV1 reversibility (%) (n = 64)*	11.3 ± 12.2	9.3 [3.3, 15.2]	8.7 [2.2, 14.6]	.36	5 [1, 7.4]	.27	11.3 [7.1, 28]	.31
TLC (L), median [IQR] (n = 68)*	6.1 [5.4, 7.1]	6 [4.9, 7]	6.1 [5.5, 7]	.08	6.6 [5.7, 7.5]	.22	6 [5.6, 6.8]	.11
% predicted (n = 68)*	106 [96.3, 116	105 [94, 111.2]	108 [96.1, 117]	.20	109 [101, 114]	.40	115 [99.8, 126]	**.01**
RV (L), median [IQR] (n = 69)*	2.9 [2.2, 3.5]	2.7 [2.2, 3.3]	3 [2.2, 3.6]	.39	2.9 [2.6, 3.6]	.97	3.3 [2.5, 4.2]	.66
% predicted (n = 69)*	139 [116, 162]6	135 [112.3, 157.2]	137 [114.4, 164.5]	.47	139 [126.5, 148.5]	.46	162 [128.2, 178.2]	**.01**
Rtot (kPa s/L), median[IQR]	0.4 [0.3, 0.5]	0.4 [0.3, 0.6]	0.4 [0.2, 0.5]	.06	0.3 [0.2, 0.4]	.28	0.4 [0.3, 0.6]	.71
MEF25 (% predicted) (n = 124)*	50.5 [31, 93.8]	56.5 [34, 102.2]	52 [33, 99.8]	.48	51 [38, 81]	.14	29 [19.5, 51]	**.02**
DLCO (% predicted) (n = 79)*	71.5 [62, 84]	73 [62.5, 86.5]	73 [64, 83]	.30	75.5 [64.2, 87.5]	.93	61 [47, 67]	<.001
Biomarkers								
PBEC (cells/μL), median (n = 683)*	320 (125-622)	316 (120-633)	315 (159-570)	.18	377 (133-626)	.85	295 (101-696)	.85

(continued)

TABLE I. *(Continued)*

Parameter	All	NS	ExS <10 py	*P* value vs NS	ExS 10-20 py	*P* value vs NS	ExS >20 py	*P* value vs NS
FeNO (ppb), mean ± SD (n = 640)*	54.8 ± 50.6	56.6 ± 52.4	51.8 ± 47.6	.34	52.5 ± 54.8	.53	54.2 ± 41.9	.72
Total IgE (IE/mL), mean ± SD (n = 1129)*	568 ± 1218	531 ± 863	562 ± 1069	.69	811 ± 2181	.55	556 ± 644	.95
Comorbidities								
Allergic conditions, n (%)	342 (30.3)	212 (33.5)	69 (26.6)	.29	31 (26.5)	.56	30 (25.0)	.11
Chronic sinusitis, n (%)	571 (50.6)	328 (51.8)	130 (50.2)	.65	61 (52.1)	1.00	52 (43.3)	.09
Nasal polyps, n (%)	477 (42.3)	273 (41.1)	108 (41.7)	.70	51 (43.6)	1.00	45 (37.5)	.27
COPD, n (%) (n = 144)*	12 (8.3)	3 (4)	2 (6.3)	1.00	4 (15.4)	.13	3 (27.4)	**.03**
Obesity, n (%)	332 (29.4)	155 (24.5)	87 (33.6)	**.007**	46 (39.3)	**<.001**	44 (36.7)	**.009**
Biologic therapy								
Omalizumab, n (%)	158 (14)	91 (14.4)	29 (11.2)	.25	18 (15.4)	.89	20 (16.7)	.61
Benralizumab, n (%)	432 (38.3)	236 (37.3)	109 (42.1)	.21	45 (38.5)	.89	42 (35.0)	.71
Reslizumab, n (%)	6 (0.5)	3 (0.5)	1 (0.4)	1.00	1 (0.9)	1.00	1 (0.8)	1.00
Mepolizumab, n (%)	207 (18.3)	107 (16.9)	48 (18.5)	.63	25 (21.4)	.30	27 (22.5)	.18
Dupilumab, n (%)	326 (28.9)	196 (31.0)	72 (27.8)	.39	28 (23.9)	.16	30 (25.0)	.23

Metric variables are displayed as mean ± SD. *P* values refer to pairwise comparisons with nonsmokers by *t* tests. Categorical variables are displayed as n (%). Statistical significance was defined as $P < .05$. *P* values refer to pairwise comparisons with nonsmokers by χ^2 tests.
Lung function parameters and number of acute exacerbations are reported by median [IQR]. *P* values refer to pairwise comparisons with nonsmokers by Mann-Whitney *U* tests.
ACQ-5, Asthma Control Questionnaire; *ACT,* Asthma Control Test; *AE*, acute exacerbation; *BMI,* body mass index; *CI*, confidence interval; *COPD*, chronic obstructive pulmonary disease; *DLCO*, diffusing capacity of the lungs for carbon monoxide; *ExS*, ex-smokers; *FeNO*, fraction of exhaled nitric oxide; *FEV1 (prebronchodilator)*, forced expiratory volume in 1 second; *FVC (prebronchodilator)*, forced vital capacity; *ICS*, inhaled corticosteroids; *IQR*, interquartile range; *LABA*, long-acting β-agonist; *LAMA*, long-acting muscarinic antagonist; *mAQLQ*, Mini−Asthma Quality of Life Questionnaire; *MEF*, mean expiratory flow; *NS*, never-smokers; *OCS*, oral corticosteroids; *PBEC,* peripheral blood eosinophil count; *ppb*, parts per billion; *py*, pack-years; *Rtot*, resistance; *RV,* residual volume; *SD*, standard deviation; *TLC*, total lung capacity.
*Patients with available data.

was 13.4 ± 5.2, with 81.8% of patients showing uncontrolled asthma as per GINA assessment. At baseline, 92.1% of the patients were prescribed high-dose ICS/long-acting β-agonists, and 46.5% were on maintenance OCS (mOCS). The mean FEV1 was 2 L (64.2%), the mean FeNO was 54.8 ppb, the median PBEC was 320/μL, and 42.3% of the patients had nasal polyps. All ExS groups had a higher body mass index (BMI) than NS. No significant gender differences were observed in patients with <20 py, but among those with over 20 py, 59.2% were male. ExS had a shorter disease duration. Initially, there were no variations between the ExS and NS groups in terms of age of asthma onset, predominantly allergic asthma, mOCS use, AE frequency in the last 12 months, ACQ-5 score, mAQLQ score, biomarkers, and related conditions such as allergic diseases, chronic sinusitis, and nasal polyps. However, the mean ACT score was lower at baseline in ExS with 10 to 20 py (12.0 vs 13.6, $P = .004$) and with >20 py than in NS (11.8 vs 13.6, $P < .001$). In terms of lung function, there were no notable differences among the groups except for those with over 20 py, which showed lower median FEV1 (1.6 vs 1.9, $P = .002$), MEF25% (29 vs 57, $P = .02$), and DLCO (61 vs 73, $P = .01$) and higher TLC% predicted (115 vs 105, $P = .01$) and RV% predicted (162 vs 135, $P = .01$). ExS with 10 to 20 py had higher FVC% predicted (90 vs 82, $P = .03$). The number of patients diagnosed with comorbid COPD in addition to their asthma diagnosis was also higher in this group (27.4% vs 3.0%, $P = .03$).

Asthma control and quality of life

Significant improvements in asthma control were observed in the overall patient population as early as 16 weeks into biologic therapy. The ACT score showed significant improvements across all groups, but the greatest improvement was noted in NS with an increase of 4.22 (95% CI: 2.76-5.69) points, indicating a difference of 0.90 points compared with ExS (95% CI: 0.9-1.88, $P = .02$). This was primarily driven by the lower improvement in ACT score in the group of patients with over 20 py, which saw an increase of only 2.91 points (Table II). The odds of experiencing worse asthma control, as per GINA assessment, were estimated to be 31% higher for ExS than NS after 16 weeks (95% CI: 0.99-1.72, $P = .058$) and 4% higher after 52 weeks of biologics (95% CI: 0.73-1.48, $P = .83$). This difference was more pronounced in ExS with >20 py, who had a 58% higher risk of worse asthma control at week 16 (95% CI: 1.02-2.48, $P = .04$) (Table III). Although clinical improvement in ExS with over 20 py at week 16 appeared slightly less pronounced, as evidenced by lower ACT scores and higher risk for worse asthma control, these disparities were no longer evident after a year of biologics (Figure 1 and Tables II and III). These results were supported by similar observations for ACQ-5 and mAQLQ at week 52, showing significant improvements in all groups, without statistical significance between ExS and NS. For example, the ACQ-5 score increased by 1.04 points in NS, whereas the most substantial improvement was seen in ExS with >20 py (1.92 points). Absolute values for all outcomes at weeks 16 and 52 are presented in Tables E1 and E2 (available in this article's Online Repository at www.jaci-inpractice.org), respectively.

Exacerbations

Biologics significantly reduced the rate of AEs in all groups, regardless of smoking status or py count (Figure 1, *B*, and Table II; Tables E1 and E2, available in this article's Online Repository at www.jaci-inpractice.org). The absolute number of exacerbations decreased by a factor of 0.27 (95% CI: 0.21-0.36, $P < .001$) in NS and by a factor of 0.26 (95% CI: 0.19-0.36, $P < .001$) in ExS over the 52-week observation period (data available for 123 patients). In addition, physicians assessed changes in exacerbation frequency for each patient. The smoking status did not significantly impact the change in exacerbation

TABLE II. Regression analysis of average treatment success in patients with a history of smoking compared with never-smokers (NS) with severe asthma treated with biologics

		NS	ExS		ExS < 10 py		ExS 10-20 py		ExS > 20 py	
		vs baseline	vs baseline	vs NS	vs baseline	vs NS	vs baseline	vs NS	vs baseline	vs NS
ACT score*, w16	Point estimate; 95% CI	4.22; 2.76 to 5.69	3.33; 1.8 to 4.86	−0.9; −1.88 to 0.09	3.62; 1.97 to 5.27	−0.61; −1.53 to 0.32	3.46; 1.5 to 5.42	−0.77; −1.98 to 0.45	2.91; 0.98 to 4.84	−1.31; −2.51 to −0.11
(n = 607)	*P* value	**<.001**	**<.001**	**.02**	**<.001**	.20	**<.001**	.22	**<.001**	**.03**
ACT score*, w52	Point estimate; 95% CI	5.28; 2.78 to 7.78	4.91; 2.39 to 7.44	−0.37; −1.66 to 0.92	4.41; 1.8 to 7.02	−0.87; −2.13 to 0.39	5.45; 2.46 to 8.44	0.17; −1.4 to 1.74	4.88; 1.82 to 7.93	0.4; −2.07 to 1.26
(n = 361)	*P* value	**<.001**	**<.001**	.48	**<.001**	.18	**<.001**	.83	**<.001**	.63
ACQ-5 score*, w52	Point estimate; 95% CI	−1.04; −1.5 to −0.59	−1.48; −2.02 to −0.9	−0.43; −1.1 to 0.24	−0.95; −1.62 to −0.27	0.1; −0.5 to 0.69	−1.54; −2.31 to −0.77	− 0.50; −1.15 to 0.15	−1.94; −3.17 to −0.76	−0.89; −1.84 to 0.05
(n = 111)	*P* value	**<.001**	**<.001**	.09	**<.001**	.75	**<.001**	.13	**<.001**	.06
mAQLQ score*, w52	Point estimate; 95% CI	1.03; 0.54 to 1.51	1.41; 0.86 to 1.95	0.38; −0.31 to 1.07	1.09; 0.4 to 1.77	0.06; −0.55 to 0.68	1.61; 0.83 to 2.39	0.58; −0.08 to 1.25	1.52; 0.36 to 2.71	0.5; −0.46 to 1.45
(n = 105)	*P* value	**<.001**	**<.001**	.15	**<.001**	.84	**<.001**	.09	**.001**	.31
No. of AEs†, w52	Point estimate; 95% CI	0.27; 0.21 to 0.36	0.26; 0.19 to 0.36	0.96; 0.66 to 1.4	0.3; 0.21 to 0.43	1.09; 0.78 to 1.53	0.23; 0.13 to 0.35	0.84; 0.58 to 1.21	0.27; 0.14 to 0.5	0.98; 0.59 to 1.62
(n = 123)	*P* value	**<.001**	**<.001**	.8	**<.001**	.59	**<.001**	.35	**<.001**	.92
Reduction of DPD†, w16	Point estimate; 95% CI	0.69; 0.49 to 0.96	0.72; 0.5 to 1.03	1.04; 0.84 to 1.29	0.71: 0.48 to 1.05	1.03; 0.83 to 1.27	0.62; 0.39 to 0.98	0.91; 0.69 to 1.19	0.83; 0.54 to 1.29	1.21; 0.94 to 1.57
(n = 236)	*P* value	**.006**	**.002**	.63	**.03**	.78	**.009**	.47	.29	.14
Reduction of DPD†, w52	Point estimate; 95% CI	0.70; 0.45 to 1.09	0.56; 0.34 to 0.93	0.80; 0.54 to 1.19	0.55; 0.31 to 0.98	0.79; 0.55 to 1.14	0.54; 0.26 to 1.11	0.77; 0.48 to 1.26	0.59; 0.29 to 1.21	0.85; 0.51 to 1.39
(n = 113)	*P* value	**.04**	**.004**	.15	**.008**	.21	**.03**	.30	**.059**	.51
Change EDB†, w52	Point estimate; 95% CI	1.02; 0.82 to 1.28	1; 0.78 to 1.28	0.98; 0.71 to 1.34	0.95; 0.7 to 1.29	0.93; 0.7 to 1.23	1.13: 0.79 to 1.63	1.11; 0.81 to 1.51	0.92; 0.54 to 1.58	0.90; 0.58 to 1.39
(n = 134)	*P* value	.79	.98	.84	.67	.60	.36	.51	.69	.64
FEV1†, w16	Point estimate; 95% CI	1.1; 1.02 to 1.2	1.08; 1 to 1.18	0.98; 0.93 to 1.03	1.11; 1.01 to 1.21	1; 0.96 to 1.05	1.08; 0.97 to 1.2	0.98; 0.92 to 1.04	1.07; 0.96 to 1.18	0.97; 0.91 to 1.03
(n = 691)	*P* value	**.002**	**.02**	.39	**.004**	.85	.07	.49	.13	.29
FEV1†, w52	Point estimate; 95% CI	1.16; 1.05 to 1.27	1.19; 1.07 to 1.32	1.03; 0.96 to 1.1	1.18; 1.06 to 1.31	1.02;0.96 to 1.08	1.20; 1.05 to 1.36	1.04;0.96 to 1.12	1.19;1.04 to 1.36	1.03;0.95 to 1.12
(n = 421)	*P* value	**<.001**	**<.001**	.28	**<.001**	.53	**<.001**	.37	**.001**	.52
FVC†, w52	Point estimate; 95% CI	1.08; 1.01 to 1.16	1.12; 10.4 to 1.2	1.03; 0.94 to 1.13	1.1; 1 to 1.21	1.02; 0.93 to1.11	1.07; 0.96 to 1.19	0.99; 0.9 to 1.08	1.18; 1.01 to 1.38	1.09; 0.96 to 1.24
(n = 128)	*P* value	**.004**	**<.001**	.40	**.01**	.73	.09	.81	**.005**	.16
FEV1% FVC*, w52	Point estimate; 95% CI	−0.23; −4.78 to 4.32	3.68; −0.76 to 8.12	3.91; −1.84 to 9.66	1.06; −4.45 to 6.57	1.29; −3.86 to 6.44	4.49; −1.96 to 10.94	4.72; −0.83 to 10.27	5.49; −3.47 to 14.46	5.72; −1.56 to 13.01
(n = 117)	*P* value	.90	**.03**	.08	.62	.62	.07	.10	.11	.12
RV†, w52	Point estimate; 95% CI	0.89; 0.74 to 1.08	0.87; 0.68 to 1.1	0.97; 0.74 to 1.28	0.95; 0.7 to 1.29	1.06; 0.82 to 1.37	0.9; 0.66 to 1.22	1; 0.77 to 1.31	0.77; 0.49 to 1.2	0.86; 0.6 to 1.21
(n = 62)	*P* value	.12	.12	.77	.65	.65	.36	.98	.12	.38
TLC†, w52	Point estimate; 95% CI	1.02; 0.96 to 1.09	0.99; 0.91 to 1.07	0.97;0.89 to 1.05	0.98; 0.89 to 1.08	0.96; 0.89 to 1.04	1; 0.9 to 1.1	0.98; 0.9 to 1.06	0.98; 0.85 to 1.13	0.96; 0.9 to 1.07
(n = 60)	*P* value	**.37**	**.64**	.27	.57	.28	.93	.55	.74	.47
Rtot†, w52	Point estimate; 95% CI	1; 0.83 to 1.24	0.81; 0.65 to 1.01	0.81; 0.61 to 1.06	0.72; 0.55 to 0.96	0.71; 0.55 to 0.92	0.89; 0.65 to 1.21	0.88; 0.67 to 1.14	0.84; 0.53 to 1.34	0.83: 0.57 to 1.2
(n = 123)	*P* value	.85	**.02**	**.04**	**.003**	**.009**	.32	.33	.33	.32
PEF†, w52	Point estimate; 95% CI	1.08; 0.99 to 1.17	1.15; 1.05 to 1.25	1.07; 0.95 to 1.19	1.11; 0.99 to 1.24	1.03; 0.93 to 1.14	1.13; 1 to 1.28	1.05; 0.94 to 1.17	1.21; 1.01 to 1.45	1.12; 0.97 to 1.3
(n = 128)	*P* value	**.0201**	**<.001**	.14	**.0171**	.5755	**.0102**	.3581	**.0081**	.1308
MEF25†, w52	Point estimate; 95% CI	1.12; 0.91 to 1.39	1.2; 0.96 to 1.51	1.07; 0.8 to 1.43	1.21; 0.89 to 1.64	1.07; 0.82 to 1.41	1.17; 0.84 to 1.63	1.04; 0.78 to 1.38	1.23; 0.77 to 1.97	1.1; 0.75 to 1.6

(n = 110)	*P* value	.15	**.04**	.55	.11	.60	.22	.78	.25	.64
MEF50†, w52	Point estimate; 95% CI	1.13; 0.96 to 1.32	1.25; 1.06 to 1.48	1.11; 0.9 to 1.37	1.23; 0.99 to 1.53	1.09; 0.9 to 1.33	1.23; 0.97 to 1.55	1.09; 0.89 to 1.34	1.3; 0.92 to 1.82	1.15; 0.88 to 1.52
(n = 124)	*P* value	**.050**	**<.001**	.18	**.01**	.36	**.02**	.39	**.048**	.31
MEF75†, w52	Point estimate; 95% CI	1.08; 0.92 to 1.27	1.23; 1.04 to 1.45	1.14; 0.92 to 1.41	1.24; 1 to 1.54	1.15; 0.94 to 1.39	1.18; 0.94 to 1.5	1.09; 0.89 to 1.34	1.27; 0.9 to 1.79	1.17; 0.89 to 1.55
(n = 123)	*P* value	.19	**.001**	.12	**.02**	.18	.06	.38	.07	.26
DLCO†, w52	Point estimate; 95% CI	1.19; 0.58 to 2.42	1.02; 0.63 to 1.63	0.86; 0.4 to 1.86	1.05; 0.41 to 2.68	0.89; 0.43 to 1.81	0.88; 0.49 to 1.58	0.74; 0.41 to 1.32	1.14; 0.44 to 2.95	0.96; 0.38 to 2.44
(n = 21)	*P* value	.48	.92	.56	.88	.72	.52	.28	.69	.92
Total IgE†, w52	Point estimate; 95% CI	0.60; 0.27 to 1.35	0.58; 0.21 to 1.57	0.96; 0.37 to 2.47	0.72; 0.25 to 2.06	1.19; 0.53 to 2.7	0.64; 0.19 to 2.17	1.06; 0.42 to 2.72	0.42; 0.07 to 2.55	0.7; 0.2 to 2.47
(n = 35)	*P* value	.10	.15	.91	.40	.66	.33	.89	.20	.57
PBEC†, w16	Point estimate; 95% CI	0.16; 0.02 to 1.21	0.23; 0.03 to 1.86	1.47; 0.62 to 3.48	0.12; 0.01 to 1.06	0.78; 0.34 to 1.78	0.41; 0.04 to 4.15	2.63; 0.92 to 7.49	0.24; 0.02 to 2.48	1.56; 0.53 to 4.61
(n = 373)	*P* value	**.03**	.09	.27	**.02**	.55	.35	.07	.14	.42
PBEC†, w52	Point estimate; 95% CI	0.13; 0.02 to 0.95	0.21; 0.03 to 1.69	1.63; 0.51 to 5.22	0.32; 0.03 to 3.01	2.44; 0.79 to 7.57	0.2; 0.02 to 2.14	1.51; 0.41 to 5.56	0.15; 0.01 to 1.95	1.17; 0.27 to 5.17
(n = 188)	*P* value	**.01**	.06	.29	.20	.12	.09	.54	.07	.83
FeNO†, w16	Point estimate; 95% CI	0.78; 0.69 to 0.89	0.73; 0.63 to 0.84	0.93; 0.78 to 1.11	0.8; 0.67 to 0.97	1.02; 0.87 to 1.02	0.55; 0.43 to 0.71	0.7; 0.57 to 0.87	0.87; 0.67 to 1.12	1.11; 0.89 to 1.37
(n = 349)	*P* value	**<.001**	**<.001**	.28	**.003**	.76	**<.001**	**<.001**	.16	.35
FeNO†, w52	Point estimate; 95% CI	0.69; 0.57 to 0.83	0.64; 0.52 to 0.8	0.93; 0.72 to 1.21	0.77; 0.59 to 0.99	1.11; 0.88 to 1.4	0.5; 0.34 to 0.73	0.72; 0.53 to 0.98	0.69; 0.47 to 1.02	1.01; 0.74 to 1.38
(n = 178)	*P* value	**<.001**	**<.001**	.48	**.008**	.37	**<.001**	**.04**	**.02**	.96

Models were fit for never-smokers and all 3 ex-smoker groups; from these complete models, contrasts between never-smokers and ex-smokers were derived. Point estimates of linear logarithmic regression are to be understood as factors—eg, the estimate of 1.1 for FEV at week 16 corresponds to an estimated increase of 10%. Statistical significance was defined as $P < .05$.

ACQ-5, Asthma Control Questionnaire; *ACT*, Asthma Control Test; *AE*, acute exacerbation; *CI*, confidence interval; *DLCO*, diffusing capacity of the lungs for carbon monoxide; *DPD*, daily prednisolone dose; *EDB*, equivalent dose beclomethasone; *ExS*, ex-smokers; *FeNO*, fractional exhaled nitric oxide; *FEV1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *mAQLQ*, mini−Asthma Quality of Life Questionnaire; *MEF*, mean expiratory flow; *PBEC*, peripheral blood eosinophil count; *PEF*, peak expiratory flow; *py*, pack-years; *Rtot*, resistance; *RV*, residual volume; *TLC*, total lung capacity; *w*, weeks.

*Linear regression.

†Linear logarithmic regression.

TABLE III. Influence of smoking on asthma control, response to biologic therapy, and reduction of concomitant medication

		ExS vs NS	ExS < 10 py vs NS	ExS 10-20 py vs NS	ExS > 20 py vs NS
Change in GINA assessment of asthma control*					
w16 (n = 811)	OR; 95% CI	1.31; 0.99-1.72	1.12; 0.8-1.56	1.27; 0.82-1.96	1.58; 1.02-2.48
	P value	**.058**	.52	.29	**.04**
w52 (n = 491)	OR; 95% CI	1.04; 0.73-1.48	1; 0.65-1.53	0.96; 0.56-1.64	1.18; 0.65-2.12
	P value	.83	1.00	.88	.59
Change in frequency of exacerbations*					
w16 (n = 682)	OR; 95% CI	0.82; 0.57-1.16	1.22; 0.81-1.82	0.63; 0.34-1.1	0.71; 0.4-1.22
	P value	.26	.33	.12	.23
w52 (n = 489)	OR; 95% CI	0.99; 0.65-1.49	1.25; 0.77-2.02	0.76; 0.38-1.43	1; 0.5-1.98
	P value	.95	.36	.41	.97
Responder to biologic therapy†					
w16 (n = 616)	OR; 95% CI	0.6; 0.35-1.03	0.71; 0.37-1.42	0.52; 0.25-1.15	0.60; 0.27-1.42
	P value	.07	.32	.09	.22
w52 (n = 488)	OR; 95% CI	1.71; 0.73-4	1.08; 0.48-2.72	2.34; 0.65-15.06	1.98; 0.54-12.81
	P value	.21	.85	.26	.38
Continuation of biologic therapy†					
w16 (n = 811)	OR; 95% CI	0.71; 0.44-1.16	0.74; 0.41-1.35	0.62; 0.32-1.31	0.79; 0.37-1.82
	P value	.17	.31	.19	.55
w52 (n = 488)	OR; 95% CI	1.33; 0.61-2.9	1.11; 0.49-2.78	1.11; 0.39-3.96	1.91; 0.52-12.37
	P value	.47	.80	.86	.40
Reduction of concomitant asthma medication†					
w16 (n = 812)	OR; 95% CI	0.98; 0.73-1.32	1.08; 0.76-1.54	0.87; 0.55-1.38	1; 0.63-1.6
	P value	.91	.65	.56	.99
w52 (n = 489)	OR; 95% CI	0.73; 0.5-1.08	0.88; 0.55-1.39	0.83; 0.46-1.51	0.54; 0.27-1.04
	P value	.12	.58	.55	.07

Statistical significance was defined as $P < .05$

CI, Confidence interval; *ExS*, ex-smokers; *GINA*, Global Initiative for Asthma; *NS*, never-smokers; *OR*, odds ratio; *py*, pack-years; *w*, weeks.

*Ordinal logistic regression.

†Binary logistic regression.

frequency already at week 16 after initiating biologics (OR: 0.82, 95% CI: 0.57-1.16, $P = .26$), and this trend persisted at the 12-month mark (OR: 0.99, 95% CI: 0.65-1.49, $P = .95$) (Table III). Notably, ExS did not exhibit a higher severe exacerbation rate, which led to hospitalization in the first year of biologics (n = 28, estimate [est.] 0, $P = 1.00$).

Oral corticosteroid use

At the beginning of the study, 46.5% of the patients were using mOCS, a pattern that was consistent across all groups (Table I). During follow-up, the number of patients relying on mOCS decreased in a similar fashion across all groups (Figure 1, *C*; Table E3, available in this article's Online Repository at www.jaci-inpractice.org). Importantly, none of the ExS groups experienced any disadvantage in terms of reducing their daily OCS dose after 1 year of treatment. By week 16, the daily prednisolone equivalence dose underwent a reduction by a factor of 0.69 in NS and a factor of 0.72 in ExS. In patients with >20 py, the reduction in the daily OCS dose was slightly less pronounced (factor 0.83), with no statistically significant difference observed between any of the ExS groups and NS (Table II).

Lung function

NS showed a 10% increase in FEV1 (95% CI: 1.02-1.20, $P < .001$), whereas ExS with <10 py exhibited an 11% increase (95% CI: 1.01-1.21, $P = .02$) at week 16. Sustained improvements were observed at week 52, with NS achieving a 16% increase (95% CI: 1.05-1.27, $P < .001$) and ExS achieving an 18% increase (95% CI: 1.06-1.3, $P < .001$).

Interestingly, there was no discernible difference in the rate of improvement between NS and ExS even after just 16 weeks (est. 0.98, 95% CI: 0.93-1.03, $P = .39$ at week 16; est. 1.03, 95% CI: 0.96-1.1, $P = .28$ at week 52), even when comparing each py group with NS. FVC also exhibited a significant improvement in all groups by week 52 (NS: est. 1.08, 95% CI: 1.01-1.16, $P < .001$; ExS: est. 1.12, 95% CI: 1.04-1.2, $P < .001$), without notable differences between them. Although the FEV1/FVC ratio showed a more pronounced improvement in ExS, this did not reach statistical significance compared with NS. Airway Rtot improvement was more prominent in ExS, particularly in patients with <10 py. By week 52, significant improvements were observed in PEF and MEF50 across all groups, with no relevant variations. Notably, RV and TLC showed no significant improvement, and there were no statistically significant differences between groups. Although patients with >20 py showed lower baseline DLCO than NS, all groups displayed similar changes in DLCO during follow-up (Figure 2 and Table II). In summary, as anticipated, baseline emphysema-associated parameters were less favorable in the groups with higher py counts, but improvements in pulmonary function testing were consistent regardless of the py count.

Biomarkers

All groups had comparable levels of PBEC, FeNO, and total IgE at baseline, although in ExS, FeNO tended to be lower and

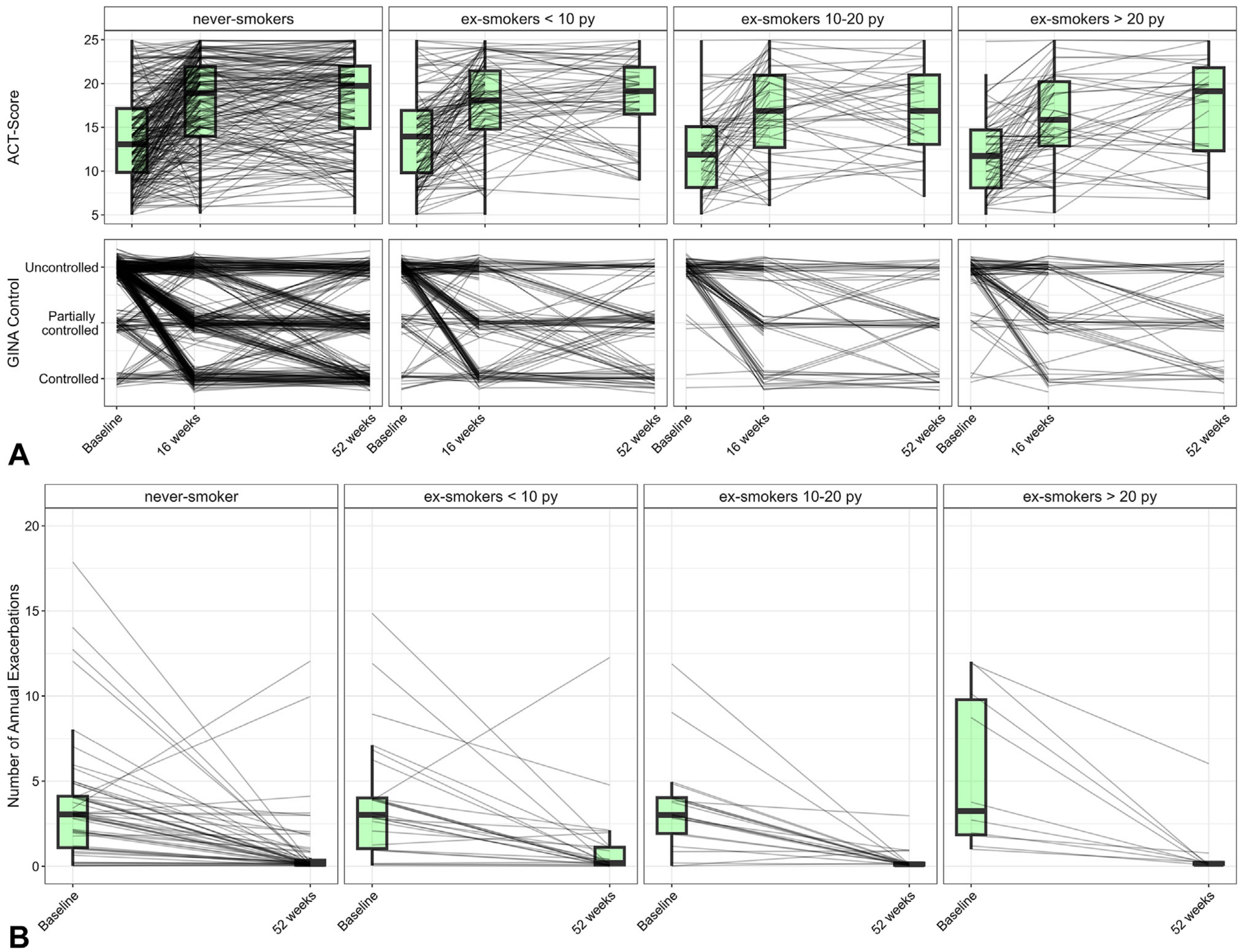

FIGURE 1. Change in asthma control, exacerbation rate, and OCS use over 1 year under biological therapy. (**A**) Change in ACT score and GINA assessment of asthma control. Data were jittered for better visibility. (**B**) Change in number of exacerbations over the follow-up period. (**C**) Daily prednisolone equivalence dose during follow-up and percentage of patients treated with OCS at 16 and 52 weeks. *ACT*, Asthma Control Test; *GINA*, Global Initiative for Asthma; *OCS*, oral corticosteroids; *py*, pack-years.

total IgE levels tended to be higher ($P > .05$). PBEC decreased significantly in NS and in patients with <10 py at week 16 and in NS at week 52. However, the difference between NS and each ExS group was not significant (est. 0.93, 95% CI: 0.72-1.21, $P = .48$). In this population selected for biologics, we observed lower baseline FeNO levels in ExS than in NS, with a 0.93-fold difference, although this disparity was not statistically significant. Furthermore, FeNO reduction was similar in all ExS groups compared with their baseline levels (Figure 3 and Tables II; Tables E1 and E2, available in this article's Online Repository at www.jaci-inpractice.org). There were no statistically significant differences in total IgE levels within each group compared with baseline and between the various ExS groups and NS.

Response to biologics

Physicians evaluated response to biologics and asthma medication reduction, including beclomethasone dose changes at 4 and 12 months. No group differences were observed as indicated in Table III.

Table IV provides the percentages of patients among ExS and NS regarding each of the endpoints at week 52. Noteworthy findings include an improvement of ≥100 mL in FEV1 in 32.2% of NS and 34.1% of ExS, a decrease in the exacerbation rate of over 50% in 79.2% of NS and 80.4% of ExS ($P = 1.00$), and a reduction of ≥50% in the OCS dose in 82.9% of NS and 74.2% of ExS (all) (OR: 0.9, 95% CI: 0.6-1.3, $P = .58$). Furthermore, 23.1% of NS and 25% of ExS ($P = 1.00$) showed improvement in all listed criteria.

No significant difference in BARS was found between 277 NS and 205 ExS (median BARS: 2 [0-3] and 1.67 [0-3], respectively, $P = .44$). The consistency was also observed for BARS-L, with both groups having a median BARS of 1 [0-2] (99 NS, 72 ExS, $P = .994$). Among 443 NS, 32% were in remission at week 52, compared with 29% among 314 ExS ($P = .49$).

Sensitivity analyses

To assess potential bias from loss to follow-up, baseline GINA asthma control, ACT scores, and FEV1% were compared between patients presenting after 16 or 52 weeks and those who did

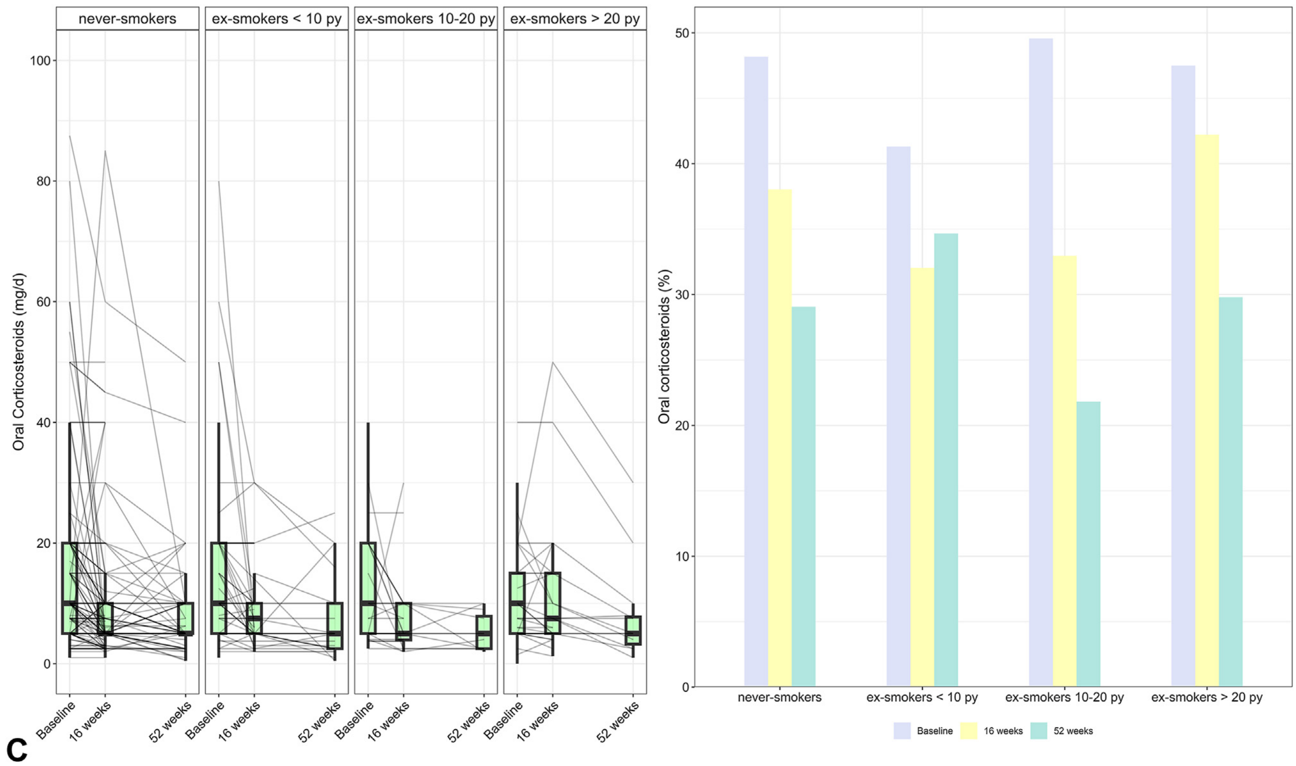

FIGURE 1. (*CONTINUED*).

not. At 16 weeks, these variables were also compared between patients presenting at 52 weeks and those who did not.

No significant differences in baseline distributions were observed between the overall population and patients completing 1 year of follow-up, supporting the validity of long-term results. Short-term results may be biased, but no consistent pattern emerged: patients with better asthma control or higher baseline FEV1 were less likely to present at 16 weeks, whereas patients with higher ACT scores at 16 weeks were more prone to present at week 52. Data are shown in Table E4 in this article's Online Repository at www.jaci-inpractice.org.

Safety

Overall, 14 patients (1.2%) reported 18 adverse events: 8 with mepolizumab, 2 with dupilumab, 6 with benralizumab, and 2 with omalizumab. Dupilumab patients experienced 3 serious adverse events: transient vision loss, uveitis, and severe conjunctivitis. The most common adverse events were increased atypical lymphocytes, joint pain, and headache (Table E5, available in this article's Online Repository at www.jaci-inpractice.org).

DISCUSSION

This study examined the influence of smoking on outcomes in a substantial group of patients with severe asthma who have a history of smoking and are undergoing treatment with biologics. We particularly focused on categorizing them by the number of py. In our patient registry, we found that 44% of the individuals receiving biologics had a smoking history. This percentage is significantly higher than what was observed in randomized controlled trials of biologics, where, for example, the CALIMA Study on benralizumab reported that only 24% of the study population had a history of smoking, with an average of 5 py.[7] Real-world data on the fraction of candidates for biologics with a history of smoking vary between 17.8% and 50%.[27,28]

Surprisingly, smoking status did not appear to impact changes in asthma control, the number of exacerbations, lung function, or biomarker levels after 4 months and 1 year of treatment with various biologics. A Danish registry study of 724 patients on biologics showed similar improvements in ACQ-5, FEV1, and reductions in exacerbations and mOCS, regardless of smoking status.[29]

Furthermore, smoking status seemed not to influence the decision to proceed with prescribed biologics. This was observed in a patient population that initially had few differences compared with NS in terms of baseline characteristics. It is noteworthy that patients with a smoking history tended to be older, had a higher BMI, and exhibited lower FEV1 and DLCO, with statistically significant differences for those with over 20 py. However, despite these variations, all groups demonstrated comparability in terms of early-onset asthma, bronchodilator response, the expression of T2-inflammation, OCS use, and exacerbation frequency.

The ACT score was lower at baseline among patients with >10 py, and we also observed a slower improvement in ACT scores 4 months after beginning of biologic therapy. Importantly, these ACT scores improved comparably to those in NS after 12 months of biologics. In addition, FEV1 demonstrated better improvement in NS and patients with <10 py at week 16, but no discernible differences between all groups after 1 year. These findings suggest that biologics are effective in patients with a smoking history and clinically relevant asthma features, even in

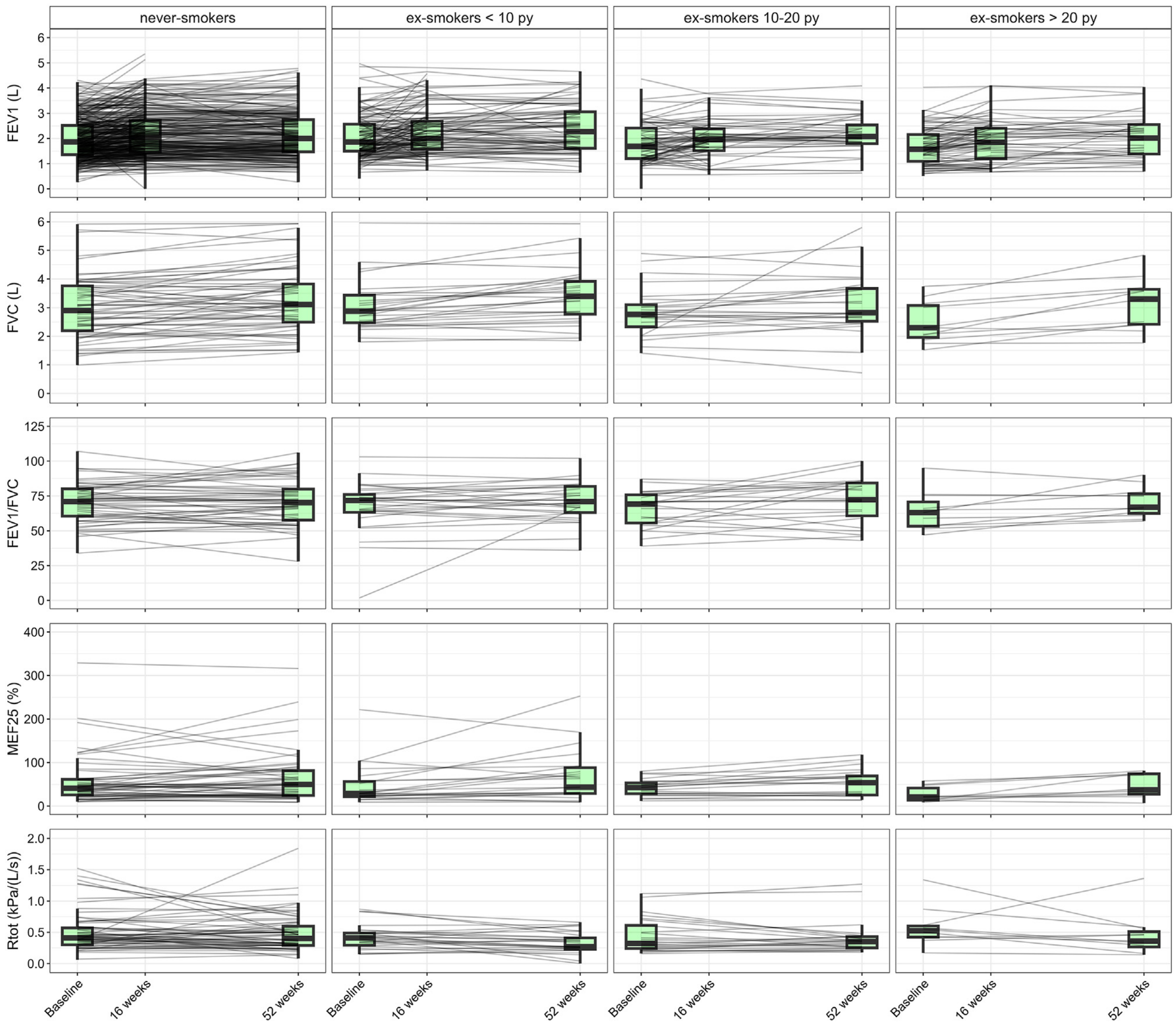

FIGURE 2. Change in lung function parameters at 16 and 52 weeks in never-smokers and ex-smokers treated with biologics. In the subfigure of Rtot, one outlier was removed for better visibility. *FEV1 (prebronchodilator)*, Forced expiratory volume in 1 second; *FVC (prebronchodilator)*, forced vital capacity; *MEF*, mean expiratory flow; *Rtot*, resistance; *TLC*, total lung capacity.

those with over 10 py, regardless of whether they have been diagnosed with COPD.

Notably, there was no difference in the daily prednisolone dose reduction in ExS compared with NS, although ExS with >20 py showed a tendency for a lower dose reduction. In comparison with randomized trials, a higher percentage of patients in our study were on mOCS with higher daily doses, yet our data align with other real-world studies.[30]

Expression of T2-inflammation was similar across all groups, suggesting that patients who exhibit measurable T2-inflammation despite a history of smoking may still be suitable candidates for biologics. Improvement in PBEC was more prominent in NS and ExS with <10 py at week 16, although the difference between ExS and NS was not statistically significant. Despite conflicting results on the effect of smoking on PBEC, our study indicates that in carefully characterized patients with a smoking history, the efficacy of biologics is similar as in NS.

This aligns with the findings regarding dupilumab's response in patients with COPD with T2 inflammation.[31]

Furthermore, the py count did not impact the reduction of concomitant asthma medication including changes in the equivalent dose of beclomethasone during therapy (Table III). Therefore, smoking' impact on responsiveness to ICS treatment obviously does not persist after smoking cessation.

FeNO levels are lower in asthmatic smokers and ExS than in NS,[32,33] which was also evident at baseline in our study population, although the disparity was not statistically significant. However, this did not hinder the improvement of FeNO levels under biologics, and we also did not observe differences related to the number of py. Smoking cessation is associated with an

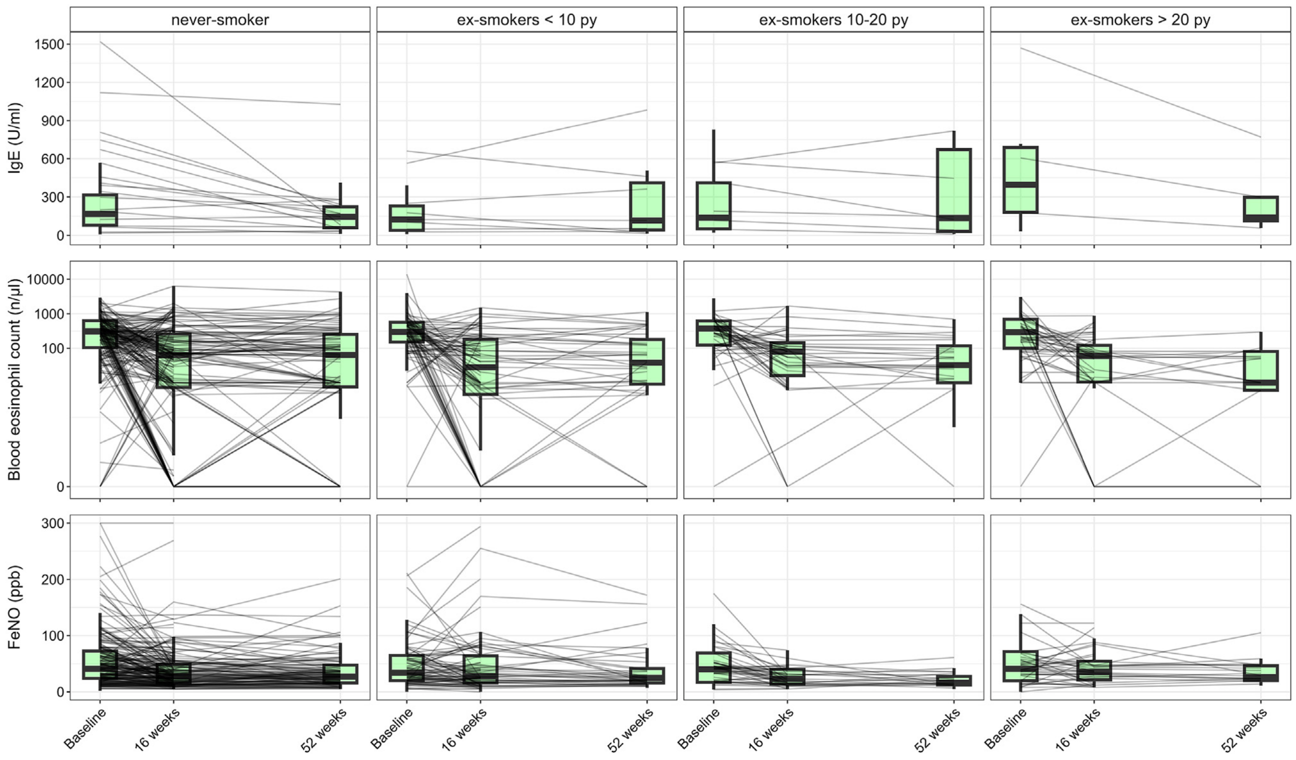

FIGURE 3. Change in blood eosinophil count and FeNO at 16 and 52 weeks in never-smokers and ex-smokers treated with biologics. *FeNO*, Fraction of exhaled nitric oxide.

TABLE IV. Percentage of response to biologic therapy after 52 weeks of treatment with odds ratios (OR) and confidence intervals (CI) for comparison of ex-smokers (ExS) to never-smokers (NS)

	n	NS (%)	ExS (%)	*P* value	OR (CI); ExS vs NS
ACT increase ≥3 points	361	63.9 (133/208)	61.4 (94/153)	.71	0.90 (0.58, 1.39)
ACQ-5 decrease >0.5 points/mAQLQ increase > 0.5 points	109	75 (42/56)	79.2 (42/53)	.77	1.27 (0.52, 3.18)
FEV1 increase ≥100 mL	423	55.4 (134/242)	55.8 (101/181)	1.00	1.02 (0.69, 1.50)
≥50% reduction of exacerbations	109	79.2 (42/53)	80.4 (45/56)	1.00	1.07 (0.42, 2.76)
≥50% reduction of OCS dose	66	82.9 (29/35)	74.2 (23/31)	.58	0.60 (0.17, 1.95)
Improvement in ≥1 criteria	29	100 (13/13)	93.8 (15/16)	1.00	0 (0, Inf.)
Improvement in all criteria	29	23.1 (3/13)	18.8 (3/16)	1.00	0.77 (0.12, 4.95)

OR <1 denotes a smaller proportion of improvement in ExS compared with smokers.

ACQ-5, Asthma Control Questionnaire; *ACT*, Asthma Control Test; *FEV1*, forced expiratory volume in 1 second; *Inf.*, infinitive; *mAQLQ*, mini−Asthma Quality of Life Questionnaire; *OCS*, oral corticosteroids.

increase in FeNO,[34] and the duration of smoking cessation could potentially influence our results; however, these data were not available. While interpreting FeNO values with caution in the presence of smoking exposure, it is reasonable to assume that ExS eligible for biologics demonstrate FeNO levels comparable to those of NS and experience similar FeNO reductions. Like previous studies, total IgE levels tended to be higher in ExS at baseline, although no statistically significant differences were observed.[35,36] Nevertheless, the improvement in total IgE levels under biologics was not affected by smoking status. It is important to note, though, that only 35 patients had IgE data at week 52.

The impact of smoking on biological response has also been analyzed in other inflammatory disorders. A Swedish registry study (535 patients) found that smokers with early rheumatoid arthritis were less likely to respond to methotrexate and TNF antagonists, while past smoking had no effect.[37] Another study of 154 patients with rheumatoid arthritis showed that a history of smoking predicted poor response to TNF antagonists, with treatment failure linked to the intensity of prior smoking, regardless of smoking status at therapy start.[38] In patients with Crohn disease on TNF antagonists, smoking predicts relapse, but quitting reduces relapse rates to those of NS.[39]

This study's strength lies in its analysis of a substantial patient cohort treated with 5 different biologics, as well as in the consistent confirmation of findings regarding the impact of smoking across various clinical aspects of severe asthma.

However, it is important to acknowledge several limitations, mainly due to the real-life nature of the registry. Variations in sample size occur because of missing values and loss to follow-up for individual patients. In addition, this study is constrained by the lack of information on the duration of smoking cessation. Future studies should collect more comprehensive smoking history data, including the time since smoking cessation, to better understand its impact on treatment outcomes and biomarker levels in patients with severe asthma. We also acknowledge a study limitation due to potential misclassification of py, as smoking history relies on patient self-reporting. Furthermore, due to the small number of active smokers, the findings in this population lack statistical power. However, these exploratory results warrant further investigation with a larger cohort. Only 0.5% (6 patients) of the study population was treated with reslizumab. Although the results seem similar to other biologics, the sample size is too small to conclude. More studies are needed to evaluate reslizumab in patients with a smoking history.

Our sensitivity analysis compared baseline GINA asthma control, ACT scores, and FEV1% between patients presenting after 16 or 52 weeks and those lost to follow-up. No significant baseline differences were found for 1-year follow-up, supporting the validity of long-term findings. However, short-term results may be biased, as patients with better baseline asthma control or FEV1% were less likely to present at 16 weeks, and higher ACT scores at 16 weeks predicted follow-up at 52 weeks. This suggests that the 16-week data may slightly underestimate the overall improvement in the cohort. Despite these potential short-term biases, the lack of a consistent pattern in loss to follow-up and the similarity in baseline characteristics for long-term participants indicate that our primary conclusions remain robust. Measures to minimize loss to follow-up in future studies should be prioritized. Strategies include enhancing mechanisms to retain and contact participants, gathering comprehensive contact details at registry inclusion, emphasizing follow-up importance, using diverse data collection methods (eg, email and phone), enhancing staff training, and offering financial incentives for clinic visits. The insights gained from these limitations will inform future study designs.

CONCLUSION

After 1 year of biologics, patients with a history of smoking demonstrated similar improvements in asthma control, exacerbation rates, lung function, and biomarkers as NS. Previous smoking has no long-term impact on the pathomechanisms targeted by the various biologics. This study offers valuable insights into biological treatment outcomes for patients with a smoking history and characterizes a specific population of individuals with severe asthma who can benefit from this therapy. This might help identify patients for upcoming severe asthma trials and clarify the impact of smoking on asthma, particularly regarding T2-inflammation.

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DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work the authors used ChatGPT in order to improve readability and language in this work. After using this, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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ONLINE REPOSITORY

TABLE E1. Clinical characteristics of the patients treated with biologic therapy at week 16, stratified by smoking status

Parameter	All	NS	ExS < 10 py	*P* value vs NS	ExS 10-20 py	*P* value vs NS	ExS > 20 py	*P* value vs NS
GINA assessment of asthma control (n = 811)								
Controlled, n (%)	206 (25.4)	119 (26.3)	53 (29.8)	.26	18 (19.8)	.13	18 (18)	.08
Partially controlled, n (%)	292 (36)	174 (38.4)	56 (31.5)		31 (34.1)		31 (34.8)	
Uncontrolled, n (%)	313 (38.6)	160 (35.3)	69 (38.8)		42 (46.2)		42 (47.2)	
ACT score, mean ± SD (n = 607)	17.6 ± 5.4	18.1 ± 5.4	17.8 ± 5.1	.39	16.6 ± 5.9	.06	15.8 ± 5.3	.001
Daily equivalent prednisolone dose (mg/d), mean ± SD (n = 236)	9.9 ± 10.8	10.2 ± 12.3	9.7 ± 7.4	.27	7.5 ± 6.7	.30	11 ± 10.8	.28
FEV1 (L), median [IQR] (n = 691)	2 [1.5, 2.6]	2 [1.5, 2.8]	2 [1.6, 2.7]	.54	2 [1.5, 2.4]	.11	1.9 [1.2, 2.4]	**.02**
PBEC (cells/μL), median [IQR] (n = 373)	60 [8.2, 186.9]	64 [6.5, 218.6]	34 [5.5, 180.2]	.25	81.8 [26, 139.1]	.35	60 [11.6, 122]	.96
FeNO (ppb), mean ± SD (n = 349)	39.7 ± 39.1	39.2 ± 37.3	46.7 ± 52.5	.81	25.4 ± 14.9	**.03**	43 ± 29.4	.20
Change in frequency of AEs (n = 682)								
Reduced, n (%)	476 (69.8)	261 (69.2)	93 (64.1)	.31	60 (77.9)	.24	60 (74.7)	.61
No change, n (%)	176 (25.8)	98 (26)	47 (32.4)		13 (16.9)		13 (21.7)	
Increased, n (%)	30 (4.4)	18 (4.8)	5 (3.4)		4 (5.2)		4 (3.6)	
Responder to biologic therapy, n (%) (n = 616)	552 (89.6)	314 (91.5)	117 (88.6)	.42	60 (84.5)	.11	60 (87.1)	.35
Continuation of biologic therapy, n (%) (n = 811)	734 (90.5)	417 (91.9)	158 (89.3)	.38	79 (86.8)	.18	79 (89.9)	.69
Reduction of concomitant asthma medications, n (%) (n = 812)	373 (45.9)	207 (45.6)	86 (48.3)	.60	39 (42.9)	.77	39 (46.1)	1.00

Data include the GINA assessment of asthma control, ACT scores, daily equivalent prednisolone doses, FEV1, PBEC, FeNO, changes in AE frequency, responder status, continuation of biologic therapy, and reductions in concomitant asthma medications. These data are analyzed with respect to smoking status, comparing outcomes between NS and ExS with varying py histories. Values are expressed as mean ± SD, median [IQR], or count (%), as appropriate. Statistical significance was defined as $P < .05$.
ACT, Asthma Control Test; *AE*, acute exacerbation; *ExS*, ex-smokers; *FeNO*, fraction of exhaled nitric oxide; *FEV1 (prebronchodilator)*, forced expiratory volume in 1 second; *GINA*, Global Initiative for Asthma; *IQR*, interquartile range; *NS*, never-smokers; *PBEC,* peripheral blood eosinophil count; *py*, pack-years; *SD*, standard deviation; *TLC*, total lung capacity.

TABLE E2. Clinical characteristics of the patients treated with biologic therapy at week 52, stratified by smoking status

Parameter	All	NS	ExS < 10 py	*P* value vs NS	ExS 10-20 py	*P* value vs NS	ExS > 20 py	*P* value vs NS
GINA assessment of asthma control (n = 491)								
Controlled, n (%)	171 (34.8)	106 (36.7)	35 (34.7)	.09	17 (30.9)	.58	17 (28.3)	.47
Partially controlled, n (%)	173 (35.2)	91 (31.5)	43 (42.6)		21 (38.2)		21 (39.1)	
Uncontrolled, n (%)	147 (29.9)	92 (31.8)	23 (22.8)		17 (30.9)		17 (32.6)	
ACT score, mean ± SD (n = 361)	18.5 ± 5.2	18.7 ± 5.2	18.8 ± 5	.95	18.4 ± 4.9	.60	17.2 ± 6	.17
ACQ-5 score, mean ± SD (n = 111)	1.8 ± 1.3	1.8 ± 1.2	1.9 + 1.5	.99	1.5 ± 1.2	.33	1.3 ± 1.1	.23
mAQLQ score, mean ± SD (n = 105)	4.9 ± 1.4	4.8 ± 1.4	4.8 ± 1.4	.98	5.2 ± 1.3	.20	5 ± 1.4	.88
No. of AEs, median [IQR] (n = 123)	0 [0, 0.5]	0 [0, 0]	0 [0, 1]	.40	0 [0, 0]	.40	0 [0, 0]	.77
Equivalent dose beclomethasone (µg), median [IQR] (n = 134)	1050 [656.2, 2000]	1000 [500, 2000]	1500 [500, 2000]	.92	2000 [1000, 2000]	.09	1050 [1000, 2000]	.68
Daily equivalent prednisolone dose (mg/d), mean ± SD (n = 113)	8.3 ± 8.3	8.9 ± 9.1	7.7 ± 7.8	.20	5.4 ± 3.1	.17	8.4 ± 8.7	.65
FEV1 (L), median [IQR] (n = 421)	2 [1.5, 2.8]	2 [1.5, 2.8]	2.3 [1.6, 3]	.054	2.1 [1.8, 2.5]	.62	2.1 [1.4, 2.6]	.58
FVC (L), median [IQR] (n = 128)	3.2 [2.5, 3.8]	3.1 [2.5, 3.8]	3.4 [2.8, 3.9]	.38	2.8 [2.5, 3.7]	.70	3.3 [2.4, 3.6]	.79
FEV1% FVC (n = 117)	71 [61, 82]	70.2 [57.7, 79]	70 [62.8, 81]	.87	72.3 [60.7, 84.2]	.71	66.9 [62.5, 76.6]	.95
RV (L), median [IQR] (n = 62)	2.9 [2.2, 3.3]	2.6 [1.9, 3.3]	3 [2.3, 3.5]	.34	3 [2.7, 3.2]	.17	3 [2.4, 3.6]	.52
TLC (L), median [IQR] (n = 60)	6.3 [5.4, 7.1]	6.2 [5, 7.1]	6.2 [5.6, 7.1]	.74	6.3 [5.7, 7.3]	.52	6.7 [5.6, 6.8]	.81
Rtot (kPa s/L), median [IQR] (n = 123)	0.4 [0.3, 0.5]	0.5 [0.3, 0.7]	0.3 [0.2, 0.4]	.03	0.3 [0.2, 0.4]	.12	0.4 [0.3, 0.5]	.70
PEF (L), median [IQR] (n = 128)	5.6 [4.2, 7.1]	5.6 [4.2, 7]	6 [5, 7.3]	.34	5.3 [3.9, 7]	.48	5.5 [4.1, 6.1]	.56
MEF25 (L), median [IQR] (n = 110)	0.6 [0.3, 1]	0.7 [0.3, 1]	0.6 [0.4, 1.2]	.84	0.5 [0.4, 0.9]	.57	0.4 [0.3, 0.6]	.10
MEF50 (L), median [IQR] (n = 124)	1.8 [1, 2.8]	2 [0.9, 2.8]	1.9 [1.2, 3.2]	.56	1.6 [1, 2.8]	.71	1.4 [1, 1.8]	.21
MEF75, median [IQR] (n = 123)	3.7 [2.4, 5.4]	3.7 [2.3, 5.3]	4.2 [2.8, 6]	.28	3.3 [2.5, 5.6]	.98	2.6 [2.3, 4.3]	.35
DLCO (% predicted), median [IQR] (n = 21)	79 [65, 86]	87 [79, 91.8]	71.5 [70.2, 72.8]	.33	77.5 [63.5, 81.5]	.09	66 [65.5, 66.5]	.33
PBEC (cells/µL), median [IQR] (n = 188)	51.9 [8.9, 180]	60.8 [7.1, 242.5]	28.9 [9.1, 141.1]	.71	50.3 [12.9, 121.6]	.92	30 [6, 81.2]	.07
FeNO (ppb), median [IQR] (n = 178)	27 [16, 44]	28 [16, 45]	26 [16, 49.5]	.83	20 [14, 31.5]	.09	29 [20.5, 47.5]	.52
Total IgE, mean ± SD (n = 35)	231.9 ± 273.6	186.8 ± 227.3	255.4 ± 339.6	.74	264.7 ± 312	1	375 ± 362.7	.26
Change in frequency of AEs (n = 489)								
Reduced, n (%)	336 (68.7)	198 (68.8)	66 (65.3)	.25	40 (74.1)	.70	40 (69.6)	.47

No change, n (%)	133 (27.2)	81 (28.1)	28 (27.7)		13 (24.1)		13 (23.9)	
Increased, n (%)	20 (4.1)	9 (3.1)	7 (6.9)		1 (1.9)		1 (6.5)	
Responder to biologic therapy, n (%) (n = 488)	454 (93)	266 (92.4)	92 (92)	1	52 (96.3)	.45	52 (95.7)	.62
Continuation of biologic therapy, n (%) (n = 488)	451 (92.4)	265 (92)	92 (92)	1	50 (92.6)	1	50 (95.7)	.57
Reduction of concomitant asthma medications, n (%) (n = 489)	226 (46.2)	139 (48.3)	47 (46.5)	.85	24 (44.4)	.71	24 (34.8)	.12

Data include the GINA assessment of asthma control, ACT, ACQ-5, and mAQLQ scores; AEs; daily equivalent doses of beclomethasone and prednisolone; lung function (FEV1, FVC, FEV1/FVC, RV, TLC, PEF, MEF25%, MEF50%, MEF75%, DLCO, PBEC, FeNO, and IgE); changes in AE frequency; responder status; continuation of biologic therapy; and reductions in concomitant asthma medications.

These data are analyzed with respect to smoking status, comparing outcomes between NS and ExS with varying py histories. Values are expressed as mean ± SD, median [IQR], or count (%), as appropriate.

ACQ-5, Asthma Control Questionnaire; *ACT,* Asthma Control Test; *AE*, acute exacerbation; *BMI,* body mass index; *COPD*, chronic obstructive pulmonary disease; *DLCO*, diffusing capacity of the lungs for carbon monoxide; *ExS*, ex-smokers; *FeNO*, fraction of exhaled nitric oxide; *FEV1 (prebronchodilator)*, forced expiratory volume in 1 second; *FVC (prebronchodilator)*, forced vital capacity; *GINA*, Global Initiative for Asthma; *ICS*, inhaled corticosteroids; *IQR*, interquartile range; *mAQLQ*, Mini−Asthma Quality of Life Questionnaire; *MEF*, mean expiratory flow; *NS*, never-smokers; *OCS*, oral corticosteroids; *PBEC,* peripheral blood eosinophil count; *PEF*, peak expiratory flow; *ppb*, parts per billion; *py*, pack-years; *Rtot*, resistance; *RV,* residual volume; *SD*, standard deviation; *TLC*, total lung capacity.

TABLE E3. Number (percentage) of patients on maintenance corticosteroids during follow-up, stratified by smoking status

	All	NS	ExS < 10 py	*P* value vs NS	ExS 10-20 py	*P* value vs NS	ExS > 20 py	*P* value vs NS
Baseline	525 (46.5%)	303 (47.87)	107 (41.31)	.07	58 (49.57)	.86	57 (47.50)	.97
w16	298 (36.08)	173 (37.37)	57 (31.32)	.19	30 (32.97)	.43	38 (42.22)	.53
w52	145 (29.00)	84 (28.57)	35 (33.98)	.36	12 (21.82)	.35	14 (29.17)	1.00

Subgroups include NS, ExS with <10 py, ExS with 10-20 py, and ExS with >20 py. Data are presented as n (%), with *P* values indicating comparisons between each ExS subgroup and NS at baseline, week 16 (w16), and week 52 (w52).
ExS, Ex-smokers; *NS*, never-smokers; *py*, pack-years.

TABLE E4. Sensitivity analysis of GINA assessment of asthma control, ACT scores, and FEV1% across follow-up periods

Variable	Baseline vs 16 weeks	Baseline vs 52 weeks	16 weeks vs 52 weeks
GINA assessment of asthma control	Significant difference ($P < .01$). Uncontrolled patients over-represented at 16 weeks	No significant difference ($P = .69$)	No significant difference ($P = .42$)
ACT score	No significant difference ($P = .91$)	No significant difference ($P = .22$)	Significant difference ($P < .01$). Median ACT 1 point higher for 52-week presenters
FEV1%	Significant difference ($P = .02$). Median FEV1 lower for 16-week presenters	No significant difference ($P = .39$)	No significant difference ($P = .13$)

ACT, Asthma Control Test; *FEV1*, forced expiratory volume in 1 second; *GINA*, Global Initiative for Asthma.

TABLE E5. Summary of adverse events reported during treatment with biologic therapies

Reported serious adverse events	
Transient loss of vision (n = 1)	Dupilumab
Uveitis (n = 1)	Dupilumab
Severe conjunctivitis (n = 1)	Dupilumab
Reported adverse events	
Increased number of atypical lymphocytes (n = 3)	Benralizumab
Joint pain (n = 2)	Benralizumab and mepolizumab
Headache (n = 2)	Mepolizumab
Skin rash (n = 1)	Benralizumab
Allergic reaction (n = 1)	Benralizumab
Weight gain (n = 1)	Dupilumab
Mild conjunctivitis (n = 1)	Dupilumab
Circulatory problems (n = 1)	Mepolizumab
Mobility impairment (n = 1)	Mepolizumab
Paresthesias (n = 1)	Omalizumab
Sinusitis (n = 1)	Omalizumab
Tingling (n = 1)	Mepolizumab
Abdominal pain (n = 1)	Mepolizumab
Throat pain (n = 1)	Mepolizumab

Data include the frequency (n) of each adverse event and the corresponding therapy: dupilumab, benralizumab, mepolizumab, or omalizumab.